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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,442	06/28/2002	Eric Lietz	22477-712	3219

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EXAMINER	
SHIBUYA, MARK LANCE	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/069,442	LIETZ, ERIC	
	Examiner	Art Unit	
	Mark L. Shibuya, Ph.D.	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,27 and 52-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,27 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/16/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. 10069442: Claims 1-24, 27, and 52-54 are pending and examined. Claims 25, 26, and 28-51 are newly canceled.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1-24 and 27, in the reply filed on 8/28/2006, is acknowledged. All species requirements are withdrawn.

Priority

3. This application, 10/069,442, filed 6/28/2002, states that it is the national stage, pursuant to 35 U.S.C. 371, of PCT/US00/22078, filed 8/11/2000; which is a continuation-in-part of 09/374274, filed 8/13/1999, now US 6,251,604, issued 6/26/2001.

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent

application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/374,274, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The priority document 09/374,274, does not disclose a first and a second primer that are complementary to a 3' sequence of a sense strand and a 3' sequence of an antisense strand, both of which flank the section of the target sequence to be mutagenized, as in independent claim 1. The priority document does not disclose CDR, single-antibody, inosine residues at the 3' end, as in the dependent claims. Therefore the effective filing date is considered to the be filing date of PCT/US00/22078, filed 8/11/2000.

Information Disclosure Statement

5. The information disclosure statement (IDS), submitted on 9/16/02, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

6. The amendment to the Specification, entered 4/6/2007, recites an nucleotide/amino acid sequence in amended paragraph at line 7, which is subject to the sequence rules, but is not identified by the appropriate sequence identifier.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2, 3, 4, 5, 22, 23, 27, 52-54 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's use of the term of nucleotide sequences that are "unknown" appear to read upon a mental step. It unclear as to who or what the sequence is "unknown". Also, it is unclear as to whether the language refers to a mental step or attempts to refer to a structural limitation of the claimed product. It is not disputed that applicant may be their own lexicographer. The examiner does not argue that the term is repugnant to the usual usage in the art. Rather, it is that claims 2, 3, 4, 5, 27, 52-54 do not reasonably apprise of one skill in the art as to the metes and bounds of the claimed invention.

Claim 22 recites the limitation "the library of mutagenized polynucleotides " in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

The term "homolog" in claims 22 and 23 is a relative term which renders the claim indefinite. The term "homolog" is not defined by the claim, the specification does

not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 8, 10-13, 16-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Kumar, US 5,556,747 A; and as evidenced by Monforte, et al., US 6,051,378 A.

The claims are drawn to a method for producing mutagenized polynucleotides comprising:

a single or double stranded polynucleotide target sequence, a first primer which flanks the section of the target sequence to be mutagenized;

a second primer which flanks the section of the target sequence to be mutagenized;

at least one oligonucleotide;

performing at least one cycle of primer extension amplification on the sample to form an imperfect double-stranded sequence;

and performing additional cycles to form a mutagenized double-stranded polynucleotide comprising sequences of the first and second primers and the sequence of the oligonucleotide.

The reference of Kumar, EP 0466083 A2, (IDS 9/16/2002), throughout the publication, discloses a PCR derived method for producing mutagenized polynucleotides using two flanking primers and a third mutagenic primer, which reads on the first and second primer and oligonucleotide of the instant claims (see Kumar at claim 1 and Figure 1; col. 9, line 35-col. 10, line 25, Example 1).

The flanking primers listed in col. 10, Table 1, contain restriction sites and the primers are 20-25 nucleotides in length. Therefore claims 8 and 10-13 are not novel. The PCR conditions, as taught by Kumar at Example 1, p. 7, lines 28-36), include 2 minutes at 50 degrees C, after melting, which allows both annealing of the primers and extension by the polymerase and at least 3 minutes at 72 degrees C. Therefore, claims 16, 17 and 19 are not novel. Kumar at col. 7, lines 64-65, teaches temperatures at about 50 degrees C, reading on less than 50 degrees C. Kumar discloses that more than one position of the target sequence can be mutated (see claim 14 of Kumar). Therefore claim 24 is not novel. Claims 2, 5, 6, 7, 9, 14, 15, 18 and 20-23 are dependent of claim 1, appear to be obvious in view of D1 and are considered to lack an inventive step (PCT Articles 33.2 and 33.3). Kumar, at col. 6, lines 12-19, teach homologs which have up to about 20% mismatches, reading on "homologs", (see also, above rejection under 35 USC, second paragraph) at least two inserted sequences or at least two portions of the target sequences have been deleted.

Bulges and loops would naturally and consistently result from imperfect double-stranded formed sequence, as evidenced by Monforte, et al., US 6,051,378 A, which states:

> Wild type probes are nucleic acids derived from a wild type nucleic acid sequence comprising at least one nucleotide sequence complementary to a nucleotide sequence of a target nucleic acid or a member of a set of NLFs. Wild type probes can be restriction site probes, fragmenting probes, or capture probes comprising a wild type nucleotide sequence that when hybridized to a complementary mutation-containing region of a target nucleic acid results in a base mismatch bulge or loop structure. Wild type refers to a standard or reference nucleotide sequence to which variations are compared. As defined, any variation from wild type is considered a mutation, including naturally occurring sequence polymorphisms.

Monforte, et al., at col. 12, lines 13-26.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 2-5, 27, 52-54 and 1, 8, 10-13, 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar, US 5,556,747 A and Arnold et al., US 6,153,410 A.

Kumar, US 5,556,747 A, is relied upon as set forth in the above rejection.

The use of an "unknown" target sequence or "unknown" oligonucleotides or fully random primers, are not suggested in the reference of Kumar, (see also, above rejection under 35 USC, second paragraph).

Arnold et al., US 6,153,410 A, throughout the patent, and especially at col. 6, lines 15-41 and Example 7, col. 21-28, teach that random primers can be used to prime DNA synthesis in PCR reactions; and to introduce mutations during said PCR reactions (col. 28, lines 6-33). Arnold et al. implies the use of a library of random primers col. 6, lines 12-41, and consequently the generation of a library of mutated sequences.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used methods comprising oligonucleotide of random and unknown oligonucleotide unknown target sequence or unknown oligonucleotides or fully random primers.

One of ordinary skill in the art would have been motivated to make and use unknown target sequence or unknown oligonucleotides or fully random primers, in order to produce diverse mutations, as taught by Arnold et al.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using unknown target sequence or unknown oligonucleotides or

fully random primers, because such oligonucleotides were known in the art, as taught by Arnold et al.

13. Claims 6, 7 and 1, 8, 10-13, 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar, US 5,556,747 A and Mattheakis et al., US 5922545 A.

Kumar, US 5,556,747 A, is relied upon as set forth in the above rejection.

Kumar does not disclose methods comprising the CDR of an antibody or a sequence encoding a single-chain antibody.

Mattheakis et al., US 5922545 A, throughout the patent, teach . Mattheakis state:

> The V_H and V_L sequences can be conveniently obtained from a library of V. $_H$ and V_L sequences produced by PCR amplification using V gene family-specific primers or V gene-specific primers (Nicholls et al. (1993) J. Immunol. Meth. 165: 81; W093/12227) or are designed according to standard art-known methods based on available sequence information. Typically, mouse or human V.sub.H and V.sub.L sequences are isolated. The V_H and V_L sequences are then ligated, usually with an intervening spacer sequence (e.g., encoding an in-frame flexible peptide spacer), forming a cassette encoding a single-chain antibody. Often, a library comprising a plurality of V_H and V_L sequences are used (sometimes also with a plurality of spacer peptide species represented). Frequently, a library is constructed wherein one or more of the V_H and V_L sequences are mutated to increase sequence diversity particularly at CDR residues, sometimes at framework residues. V region sequences can be conveniently cloned as cDNAs or PCR amplification products for immunoglobulin-expressing cells. For example, cells from human hybridoma, or lymphoma, or other cell line that synthesizes either cell surface or secreted immunoglobulin are used for the isolation of polyA+ RNA. The RNA is then used for the synthesis of oligo dT primed cDNA using the enzyme reverse transcriptase (for general methods see, Goodspeed et al. (1989) Gene 76: 1; Dunn et al. (1989) J. Biol. Chem. 264: 13057). Once the V-region CDNA or PCR product is isolated, it is

> cloned into a vector to form a single-chain antibody cassette. For example and not limitation, the CANTAB vector system (sold commercially by Pharmacia Biotech, Alameda, Calif.) and its variants are suitable for cloning V.sub.H and V.sub.L sequences by PCR amplification. The phagemid pSEx (Dubel et al. (1993) Gene 128: 97) and similar vectors are suitable for surface display of scFv on bacteriophage.

Mattheakis et al., col. 19, line 61-col. 20, line 27.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used methods comprising methods for mutagenizing the CDR of an antibody or a sequence encoding a single-chain antibody.

One of ordinary skill in the art would have been motivated to make and use unknown target sequence or unknown oligonucleotides or fully random primers, in order to produce diverse mutations, as taught by Mattheakis et al.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using methods comprising methods for mutagenizing the CDR of an antibody or a sequence encoding a single-chain antibody, as taught by Mattheakis et al.

14. Claims 9 and 1, 8, 10-13, 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar, US 5,556,747 A and Hu et al., US 6040157 A.

Kumar, US 5,556,747 A, is relied upon as set forth in the above rejection.

Kumar does not disclose

Hu et al., throughout the patent, and e.g., at col. 57, lines 1-10, disclose the use of primer containing an ATG sequence and another primer containing a stop codon. Hu et al., state:

> The above described 5' primer (SEQ ID NO: 19), incorporates an NdeI restriction site and the above described 3' Primer (SEQ ID NO:20), incorporates an Asp718 restriction site. The 5' primer (SEQ ID NO: 19) also contains an ATG sequence adjacent and in frame with the VEGF-2 coding region to allow translation of the cloned fragment in E.coli, while the 3' primer (SEQ ID NO:20) contains one stop codon (preferentially utilized in E.coli) adjacent and in frame with the VEGF-2 coding region which ensures correct translational termination in E.coli.

Hu et al., at col. 57, lines 1-10.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used methods the use of primer containing an ATG sequence and another primer containing a stop codon.

One of ordinary skill in the art would have been motivated to make and use methods comprising the use of primer containing an ATG sequence and another primer containing a stop codon, in order to allow translation of the cloned fragment and correct translational termination, as taught by Hu et al.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using methods comprising the use of primer containing an ATG sequence and another primer containing a stop codon, because such methods were known in the art, as taught by Hu et al.

15. Claims 14, 15 and 1, 8, 10-13, 16-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar, US 5,556,747 A and Ling et al., Analytical Biochemistry, (1997), Vol. 254, pp. 157-178, (IDS filed 9/16/02).

Kumar, US 5,556,747 A, is relied upon as set forth in the above rejection.

Kumar does not disclose inosine residues at the 3' end.

Ling et al., throughout the publication an especially at pp. 167-168, teach the use of inosine residues as ambiguous degenerate base analogs to provide for mutations.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used methods comprising the use of inosine residues.

One of ordinary skill in the art would have been motivated to make and use the use of inosine residues as ambiguous degenerate base analogs to provide for mutations in order to avoid bias toward transition versus transversions, and because Ling teaches methods comprising inosine seem to be less sequence dependent than error-prone PCR methods, as taught by Ling et al.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using mutations methods comprising inosine residues, because such methods were known in the art, as taught by Ling et al.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-24, 27, and 52-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6251604.

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-27 of U.S. Patent No. 6251604 are drawn to a method for producing a library of mutagenized polynucleotides comprising:

a target sequence including a section to be mutagenized;

a first primer to the target sequence to be mutagenized;

a second primer to the target sequence to be mutagenized;

a library of oligonucleotide;

performing at least one cycle of primer extension amplification on the sample to form an imperfect double-stranded sequence;

and performing additional cycles to form a mutagenized double-stranded polynucleotide comprising sequences of the first and second primers and the sequence of the oligonucleotide.

Patent No. 6251604, teaches libraries of oligonucleotides and primers that flank target sequences.

It would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to use methods for producing mutagenized polynucleotides. One of ordinary skill in the art would have been motivated to make and use such mutagenized polynucleotides from a target sequence, because the '604 patent claims making libraries of mutagenized polynucleotides.

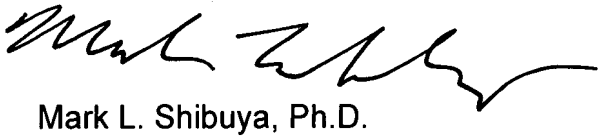
Conclusion

18. Claims 1-24, 27, and 52-54 are rejected.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Shibuya, whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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